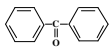
Toxicology and Carcinogenesis Studies of Benzophenone in F344 Rats and B6C3F1 Mice



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Use and Human Exposure

- Used as an additive in fragrances, cosmetics, toiletries, pharmaceuticals, insecticides, and flavor ingredients.
- High Production Volume chemical, with production exceeding one million pounds per year in the US
- Potential occupational exposure

Nomination and Selection Criteria

Nominated by the NIEHS for toxicity and carcinogenicity studies based on the potential for occupational and consumer exposure and the lack of chronic toxicity data.

Studies Performed by the NTP

- 14-Week toxicity studies (NTP, 2000)
- Genetic toxicity studies
- Single-dose toxicokinetic studies
- 2-Year toxicity and carcinogenicity
- Plasma concentrations of benzophenone in 2-year studies were measured in rats at 2 weeks and 3, 12, and 18 months and in mice at 12 months

Summary of 14-Week Feed Study Results in Rats and Mice

Exposure concentrations used : 0, 1,250, 2,500, 5,000, 10,000 and 20,000 ppm

- In rats, liver and kidney were the major organs of toxicity in males and females
- In mice, liver was the major organ of toxicity in males and females
- Increases in liver cytochrome P-450 2B isomer were observed in rats and mice along with increases in organ weights and hepatocyte hypertrophy and vacuolization

Based on these results 0, 312, 625 or 1,250 ppm exposure concentrations in diet were selected for the 2-year studies

2-Year Study Results in Rats

In-Life Observations in Rats

Survival: Survival of high dose group males was significantly reduced due to severe nephropathy.

Body Weights: Final body weights of high dose groups were more than 10% lower than controls in both males and females.

Feed Consumption: Generally lower in the high dose groups of males and females.

Clinical Findings: None other than associated with morbidity.

Lesions in Male Kidney (single and step sections combined)

	Control	312 ppm	625 ppm	1,250 ppm
Renal tubule, hyperplasia	3	11*	30**	40**
Renal tubule, adenoma	2 (4%) P<0.004[a]	2 (4%)	7 (14%)	8 (16%) **
Renal tubule, carcinoma	0	1	0	0

N=50 *p<0.05 **p<0.01 [a] trend test

Mononuclear Cell Leukemia in Rats

	Control	312 ppm	625 ppm	1,250 ppm
Males Mononuclear cell leukemia[a]	27 (54%) P=0.508[b]	41 (82%)**	39 (78%)**	24 (48%)
Females Mononuclear cell leukemia[c]	19 (38%) P=0.058	25 (50%)	30 (60%)*	29 (58%)

N=50 *P< 0.05 **P< 0.01 [a] historical range (30-68%) [b] trend test
[c] historical range (12-38%)

Histiocytic Sarcoma Incidences in Female Rats

	Control	312 ppm	625 ppm	1,250 ppm
Histiocytic Sarcoma	0 (0%) P=0.074	0 (0%)	1 (2%)	2 (4%)

N=50 [a] historical range: feed (0/460);all routes (1/1,209, range 0-2%)

Selected Non-neoplastic Lesions in Rats

Males

Kidney- Renal tubule, hyperplasia

Liver - Centrilobular hypertrophy; Degeneration, cystic; Inflammation, chronic active

Females

Kidney- Renal tubule, hyperplasia

Liver - Centrilobular hypertrophy; Bile Duct, hyperplasia; Inflammation, chronic active

2-Year Study Results in Mice

In-Life Observations in Mice

Survival: Survival of exposed males and females was similar to that of control

Body Weights: Final body weights were similar to controls except in the high dose females that were 14% less than controls

Feed Consumption: Generally similar to controls both in males and females

Clinical Findings: None

Hepatocellular Tumor Incidences in Mice

	Control	312 ppm	625 ppm	1,250 ppm
Males				
adenoma[a]	11 (22%) P=0.006[b]	15 (30%)	23 (46%)**	23(46%)**
carcinoma	8	5	6	6
hepatoblastoma	0	1	1	3
adenoma, carcinoma or hepatoblastoma	18 (36%) P=0.013	20 (40%)	25 (50%)	29 (58%)˙
Females				
adenoma[c]	5 (10%) P=0.081	4 (8%)	10 (20%)	8 (16%)

N=50, [a] historical range (12-30%) [b] trend test, [c] historical range (6-12%) ˙ < 0.05,**<.01

Histiocytic Sarcoma Incidence in Female Mice

	Control	312 ppm	625 ppm	1,250 ppm
Histiocytic Sarcoma Poly-3 test	0 (0%) P=0.032[a]	0 (0%)	5 (10%)˙ P=0.031	3 (6%) P=0.108

N=50, [a] trend test, ˙ p< 0.05, historical range (0-2% feed studies, 0-8% all routes)

Increases of Selected Non-neoplastic Lesions in Mice

Males

Liver – Hepatocyte, centrilobular hypertrophy, multinucleated, inflammation, degeneration

Kidney – Nephropathy

Nose – Olfactory epithelium, metaplasia

Spleen – Lymphoid follicle, hyperplasia, lymphoid

Testes – Mineralization

Females

Liver – Hepatocyte, centrilobular hypertrophy, inflammation

Kidney – Nephropathy, Mineralization

Nose - Olfactory epithelium, metaplasia

Spleen – Hematopoietic cell proliferation; Lymphoid follicle, hyperplasia, lymphoid

Results From Additional Studies

- Benzophenone showed no evidence of genetic toxicity *in vitro or in vivo*
- In single-dose toxicokinetic studies, the data were analyzed by non-compartmental modeling that indicated no consistent sex-related or exposure-related effects in either species
- In rat 2-year studies, sex difference was observed. The area under the plasma concentration curve versus time plots were generally higher for females

Conclusions (Rats)

- *Some evidence of carcinogenic activity* of benzophenone in male rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344 rats may have been related to benzophenone exposure
- Equivocal evidence of carcinogenic activity of benzophenone in female rats based on the marginal increased incidences of mononuclear cell leukemia and histiocytic sarcoma
- Increased incidences and/or severities of non-neoplastic lesions in the kidney and liver of both male and female rats
- Decreased incidences of mammary gland tumors in females

Conclusions (Mice)

- There was *some evidence of carcinogenic activity* in male mice based on increased incidences of hepatocellular neoplasms, primarily adenoma.
- There was *some evidence of carcinogenic* activity in female mice based on increased incidences of histiocytic sarcoma; the incidence of hepatocellular adenoma in female mice may have been related to benzophenone exposure.
- Increased incidences and/or severities of non-neoplastic lesions in the liver, kidney, nose, and spleen of both males and females.